A BIOKINETIC MODEL FOR SYSTEMIC NICKEL

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ABSTRACT

The International Commission on Radiological Protection (ICRP) is updating its suite of reference biokinetic models for internally deposited radionuclides. This paper reviews data for nickel and proposes an updated biokinetic model for systemic (absorbed) nickel in adult humans for use in radiation protection. Compared with the ICRP's current model for nickel, the proposed model is based on a larger set of observations of the behavior of nickel in human subjects and laboratory animals and provides a more realistic description of the paths of movement of nickel in the body. For the two most important radioisotopes of nickel, ^{59}Ni and ^{63}Ni, the proposed model yields substantially lower dose estimates per unit of activity reaching blood than the current ICRP model.

Key words: nickel, biokinetic model, radiological protection

INTRODUCTION

Nickel is a hard metal with chemical properties favorable for combining with iron, zinc, copper, and other metals to form alloys that are widely used in industry and consumer products, including items made of stainless steel. Nickel is an essential trace metal for many plant species, but whether it is essential to animals remains under debate (Klein and Costa, 2015). Toxic effects of stable nickel on the respiratory tract and immune system have often occurred from inhalation exposure in occupational settings. Adverse effects of nickel, particularly allergic contact dermatitis, sometimes result in non-occupationally exposed persons from handling stainless steel or nickel plated objects.

Naturally occurring nickel is a mixture of five stable isotopes: ^{58}Ni (68.08%), ^{60}Ni (26.22%), ^{61}Ni (1.14%), ^{62}Ni (3.63%), and ^{64}Ni (0.93%). Nickel has many radioisotopes but only a few with half-life greater than 30 seconds. The important radioisotopes from the standpoint of radiation protection are ^{59}Ni ($T_{1/2}$ ~100,000 y) and ^{63}Ni ($T_{1/2}$ ~100 y), which are produced by neutron activation of components in nuclear reactors and are of concern in spent nuclear fuel and radioactive wastes. Nickel-63 has several beneficial applications. For example, it has been used as a component of voltage regulators, surge protectors, electron capture detectors for gas chromatographs, and devices used to detect explosives (NUREG BR/0217 Rev1, April 2000).

The biological behavior of nickel has been investigated in a number of occupational or experimental studies. A variety of biokinetic models for nickel have been proposed for relating internal deposition of nickel to potential adverse chemical or radiological effects (e.g., Onkelinx

et al., 1973; Chausmer, 1976; Onkelinx and Sunderman (1980); Menzel, 1988; Sunderman et al., 1989; ICRP, 1981, 1993).

The systemic model for nickel currently recommended by the International Commission on Radiological Protection (ICRP) for evaluation of occupational intakes of nickel is shown in Figure 1. The model depicts one-directional flow of absorbed nickel, from blood to tissues and from tissues directly to excretion pathways. The model was intended as a mathematically convenient tool for estimating cumulative activities in tissues and the implied committed doses from intake of radio-nickel and was not designed to depict realistic paths of movement of nickel in the body.

The ICRP currently is updating its suite of biokinetic models used for assessment of doses to radiation workers from internally deposited radionuclides. The updated models, referred to as OIR (Occupational Intake of Radionuclides) models, continue a trend in recent ICRP reports toward physiological realism, particularly with regard to the paths of movement of radionuclides in the body. The OIR model structures generally include one or more compartments representing blood, depict recycling of activity between tissues and blood, and, where feasible, reflect physiological processes that influence rates of transfer of internally deposited radionuclides.

This paper reviews published biokinetic data and models for nickel in humans and laboratory animals with emphasis on the biokinetics of systemic (absorbed) nickel and proposes a biokinetic model for systemic nickel for use in radiation protection.

SUMMARY OF THE DATABASE

Observed behavior or nickel in human subjects and laboratory animals

Oral intake of nickel by humans is primarily from food since the concentration in drinking water usually is relatively low (Sunderman, 2004). Reported values for dietary intake of nickel by adult humans typically are in the range 70-300 mg d^{-1}. Controlled human studies of absorption of ingested nickel as well as comparison of reported values for dietary and urinary nickel indicate that on average less than 1% of dietary nickel is absorbed to blood; however, absorption may reach 50% for nickel ingested in drinking water after an overnight fast (Sunderman, 1993). Respiratory absorption may be the most important route of nickel uptake in some settings, particularly in industrial regions and in certain occupations. This has been demonstrated for workers in nickel refineries and electroplating shops (Doll, 1990). The percentage of inhaled nickel absorbed to blood varies with its chemical and physical form and may exceed 30% for inhalation of nickel in relatively soluble form (Sunderman, 1993).

Urinary excretion is the major route for elimination of systemic nickel (Sunderman et al., 1989; Patriarca et al., 1997). Estimates of endogenous fecal excretion of nickel vary from a few percent to 20% or more of the amount reaching blood. Nickel is also removed from the body in sweat, hair, saliva, and other typically minor excretion pathways (Sunderman, 1993).

The nickel content in the adult human body and in individual tissues has been estimated from measurements of the nickel concentration in tissues collected at autopsy. Estimates vary greatly, as illustrated in Table 1. The wide variation presumably results mainly from variation in the nickel concentration in environmental media, although measurement errors may be a contributing factor. Concentrations determined prior to about 1980 involve particularly large uncertainties due to limitations in analytical equipment, inadequate reference material for quality control, and high potential for contamination of samples (Sunderman, 1993). Since the mid-1980s the preferred analytical techniques for measurement of nickel in biological material have been Electrothermal Atomic Absorption Spectrophotometry (EAAS) and variations of Inductively Coupled Plasma Spectrometry (Rezuke et al., 1987; Sunderman, 1993; Templeton et al., 1994a, 1994b; ATSDR, 2005). The relatively low limits of detection of these techniques, along with special precautions to reduce nickel contamination during collection, processing, and analysis of samples, appear to have substantially reduced the potential errors in measurement of nickel in human tissues and fluids (Rezuke et al., 1987; Sunderman, 1993).

Templeton et al. (1994a) critically reviewed the literature on nickel concentrations in human serum, plasma, blood, and urine of healthy adult subjects without occupational intake of nickel, with the goal of establishing reference nickel concentrations. They concluded that the average concentration in serum is 0.2 $\mu g\ L^{-1}$ or lower, and the average concentration in urine is in the range 1-3 $\mu g\ L^{-1}$, depending on food and fluid intake and environmental factors.

Sunderman et al. (1989) measured the concentration of nickel in serum, urine, and feces of healthy adult human subjects following acute ingestion of elevated quantities of stable nickel in water (Experiment 1) or food (Experiment 2). Nickel was analyzed by electrothermal atomic

absorption spectrophotometry. Measurements were made from 2 days before to 4 days after administration of 12 (n=4), 18 (n=4), or 50 (n=1) µg Ni kg^{-1}, compared with normal daily intake on the order of 1-4 µg kg^{-1} by these subjects as indicated by fecal measurements prior to administration of nickel. In Experiment 1, the subjects fasted 12 h before and 3 h after drinking NiSO dissolved in water. In Experiment 2, the subjects fasted 12 h before consuming a standard American breakfast containing NiSO. In Experiment 1, absorption of nickel to blood averaged ~27% of the nickel ingested in water and 0.7% of the nickel ingested in food. The removal half-time of absorbed nickel from the body averaged 28 h. On average, urinary excretion of nickel over the observation period accounted for over 90% of absorbed nickel. Renal clearance of nickel averaged 8.3 ml min^{-1} in Experiment 1 and 5.8 ml min^{-1} in Experiment 2. These values are consistent with the mean renal clearance of 7.7 mL min^{-1} determined for 26 male workers at two electrolytic refining operations (Nieboer et al., 1992). The study did not allow quantification of endogenous fecal excretion of administered nickel.

Patriarca et al. (1997) investigated the behavior of ingested nickel in four healthy adult human subjects using the stable nickel isotope ^{62}Ni as a tracer. The mass of administered ^{62}Ni was 10 µg kg^{-1}, compared with normal daily intake of total stable nickel by these subjects of about 1-6 µg kg^{-1}based on fecal measurements. The investigators measured concentrations of ^{62}Ni in plasma, red blood cells (RBC), urine, and feces up to 5 d after administration in water. Nickel-62 concentration was determined by isotope-dilution inductively coupled plasma-mass spectrometry with ^{61}Ni (spike). The inter-individual variation in results was considerably lower than in the study by Sunderman et al. (1989), in which naturally abundant nickel was administered. Patriarca and coworkers attributed the comparatively low variability of their data to the ability to

distinguish the tracer from other sources of nickel in the tissue and fluid samples, including nickel from normal diet and nickel contamination of samples. Plasma clearance curves for the subjects of Patriarca et al. were consistent with the serum clearance curve indicated in the study of Sunderman and coworkers. However, average urinary excretion accounted only for about two-thirds of the absorbed nickel over five days in the subjects of Patriarca et al., compared with a central value of ~93% over 4 d indicated by results of Sunderman and coworkers. The data of Patriarca and coworkers indicate that total-body retention at 5 d plus losses from the body by that time via pathways other than urine accounted for about one-third of absorbed ^{62}Ni. Comparisons of the rate of fecal excretion of ^{62}Ni with fecal excretion of other markers indicated that endogenous fecal excretion of ^{62}Ni represented at most a few percent of absorbed ^{62}Ni.

Information on the early distribution and retention of systemic nickel comes mainly from animal studies. In the development of the present model, biokinetic data for nickel in laboratory animals were particularly important in the determination of transfer coefficients describing the initial uptake and early retention of nickel by kidneys, liver, and bone. No attempt was made to adjust these data for application to humans due to a sparsity of information on species dependence of nickel biokinetics.

At early times after administration the highest tissue concentration of nickel in laboratory animals usually is found in the kidneys. For example, at 24 h after oral administration of three soluble nickel compounds ($Ni(NO_3)_2$, $NiCl_2$ and $NiSO_4$) to male Wistar rats, the kidneys contained an estimated 80% of the nickel recovered in measured organs (Ishimatsu et al., 1995). Elevated concentrations at early times after administration also have been observed in lung,

pituitary, skin, adrenals, and gonads (Parker and Sunderman, 1974; Jacobsen et al., 1978; Olsen and Jonsen, 1979).

Smith and Hackley (1968) studied the nickel distribution in rats over the first 72 h after intravenous injection of carrier-free ^{63}Ni. The kidneys showed a substantially higher activity concentration than other tissues at all times. For example, the concentration ratio kidneys:liver was 18 at 0.25 h, 23 at 1 h, 32 at 2 h, 20 at 4 h, and the concentration ratio kidneys:femur was 27 at 0.25 h, 36 at 1 h, 56 at 2 h, 59 at 4 h. The total ^{63}Ni content of the kidneys was at least three times greater than that of the liver throughout the observation period. The kidneys contained at least as much ^{63}Ni as the skeleton throughout the observation period, assuming that the ^{63}Ni content of the femur was reasonably representative of the entire skeleton.

At 24 h after intravenous injection of $^{63}NiCl_2$ into rabbits the concentration of ^{63}Ni in kidneys was about 23, 18, and 29 times that in liver, bone, and muscle, respectively (Parker and Sunderman, 1974). At 24 h after intramuscular injection of $^{63}NiCl_2$ into rats the concentration of ^{63}Ni in kidneys was about 29 times that in liver and 86 times that in muscle (Sunderman et al., 1978).

Jacobson et al. (1978) studied the distribution of ^{63}Ni in tissues of the adult female mouse following intraperitoneal injection of $^{63}NiCl_2$. The activity concentration generally was higher in kidney than in liver, heart, brain, bones, and incisors during days 1-5 after injection but was lower than that of liver, bones, and incisors at 22 d.

Following intravenous injection of $^{63}NiCl_2$ into mice, the early distribution of ^{63}Ni was characterized by high concentration in connective tissue and cartilage, blood, kidney, and urinary bladder (Oskarsson and Tjalve, 1979). The highest concentration was found in kidney at 1 h, sternal cartilage at 24 h, and kidney and lungs at 5-10 d. The concentration ratio of ^{63}Ni in kidney to that in liver was about 24 at 1 h, 9 at 1 d, 3 at 5 d, and 4 at 10 d. This suggests that the kidneys initially contained substantially more activity than the liver but only slightly more by 1 d. At 5-10 d the liver contained roughly twice as much ^{63}Ni as the kidneys. In the kidneys, activity was localized in small areas of the cortex, although up to 24 h some activity was also present in the cortico-medullary zone. Activity was relatively high in the distal convoluted tubules and relatively low in the proximal convoluted tubules. Results of in vitro studies suggested that chondroitin sulfate of cartilage and keratin of skin have cation binding properties that explain the binding of $^{63}Ni(II)$ in these tissues.

A number of short-term studies of the behavior of nickel in laboratory animals indicate that nickel has a low affinity for bone, but some longer-term studies indicate that a portion of deposited nickel is removed relatively slowly. Jacobson et al. (1978) measured the distribution of ^{63}Ni in tissues of mice over 22 d following intraperitoneal injection of $^{63}NiCl_2$. The activity concentration was higher in the kidney than in other investigated organs of the adult at 1-5 d after injection but was substantially lower than that of the skull, long bone, and incisors at 22 d. English et al. (1981) measured the distribution of ^{63}Ni in rats over 90 d following intrathracheal administration of the soluble compound $NiCl_2$. Activity was readily distributed throughout the body. Activity in bone declined by two orders of magnitude from 2 h to 7 d after exposure and

thereafter declined slowly. The concentration in bone at 90 d was about 0.6% of the concentration at 2 h.

Simple compartmental analyses of systemic nickel kinetics

Onkelinx et al. (1973) performed a compartmental analysis of the early kinetics of systemic nickel based on time-dependent measurements of ^{63}Ni in rats and rabbits following a single intravenous injection of $^{63}NiCl_2$. In rats, urinary excretion averaged 78% and fecal excretion averaged 15% of injected ^{63}Ni during the first three days. In rabbits, urinary excretion averaged 78% of injected ^{63}Ni during the first 24 h. Fecal excretion of ^{63}Ni was not determined for rabbits, but biliary secretion during the first 5 h after injection averaged ~9% of the administered activity. A non-exchangeable or slowly exchangeable body reservoir (sink) was indicated by analysis of the data for rats but could not be confirmed from the less complete inventory of activity in rabbits. Parameter values for each species were developed within the compartmental model structure shown in Figure 2.

Chausmer (1976) studied the distribution and retention of ^{63}Ni following intravenous administration of $^{63}NiCl_2$ to rats. Kidney tissue was estimated to have the largest rapidly exchangeable pool during the first 16 h of the study. Compartmental analysis indicated two intracellular compartments in kidney, liver, lung and spleen and one compartment in bone. The rapid-turnover compartment in soft tissues had a half-time of several hours and a slower compartment had a half-time of severa1 days.

Sunderman and coworkers (1989) developed a biokinetic model for ingested nickel (Figure 3) as a fit to measurements of nickel in serum, urine, and feces of healthy adult human subjects (see the previous section). The model structure is a modified version of the Onkelinx model (Figure 2), with compartment V1 equated with serum and transfers to feces and the body sink removed from the model. The transfer coefficients shown in Figure 3 were based on data from Experiment 1 of the study described earlier but do not differ greatly from values based on the more variable data from Experiment 2 of that study.

As described in the previous section, the data derived in the study by Sunderman et al. (1989), and hence the model developed as a fit to that data set, are inconsistent in some respects with results of the later human study of Patriarca et al. (1997). With regard to assessment of typical biokinetics of nickel, the study by Patriarca and coworkers have the advantages of a slightly lower mass of administered nickel and the ability to distinguish their tracer from other sources of nickel in tissue and fluid samples.

The data of Patriarca are reproduced reasonably well by the variation of the model of Sunderman et al. (1989) shown in Figure 4. The modified model retains the three compartments of the Sunderman model but moves back toward the model structure proposed by Onkelinx et al. (1973) by adding a compartment representing a body sink plus fecal excretion. The modified model equates serum nickel with plasma nickel and carries over the rates of exchange between serum and tissues derived by Sunderman and coworkers. A transfer coefficient from Plasma to Urine of 3.8 d^{-1} is based on a plasma volume of 3000 ml in the reference adult male (ICRP, 2002) and renal clearance of 8 ml plasma/min, the average of the central value determined by

Sunderman et al. in their Experiment 1 and the central value determined in a study of 26 electrolytic refinery workers (Nieboer et al., 1992). The transfer coefficient from Plasma to Body sink + Feces is set at one-half the coefficient from Plasma to Urine (1.9 d^{-1}) based on the finding of Patriarca and coworkers that, on average, the portion of absorbed nickel removed in urine over 5 d was about twice the amount retained in the body or excreted along other pathways. Predictions of the modified model of Sunderman et al. are compared with observations of Patriarca and coworkers (1997) in Figures 5 and 6.

Proposed biokinetic model for systemic nickel in adult humans

The model for systemic nickel proposed here is an extension of the model shown in Figure 4 that addresses uptake and retention in specific tissues. That is, the proposed model retains the general features of nickel kinetics shown in Figure 4 including net transfer rates but divides each of the compartments "Tissues" and "Body sink + Feces" into multiple compartments representing kidneys, liver, bone, and remaining soft tissues and adds paths of movement that require the derivation of additional transfer rates. For example, in the proposed model: the rate of return of nickel to plasma from readily exchangeable nickel pools (excluding the kidneys) is set at 1.9 d^{-1} based on the transfer coefficient from Tissues to Plasma in the modified Sunderman model; the sum of transfer coefficients from plasma to tissues with a return rate of 1.9 d^{-1} is required to be 9 d^{-1} (except for rounding errors); and the proposed model retains the estimated renal clearance of 3.8 d^{-1} but depicts this as the net result of exchange between plasma and kidneys and loss of part of the nickel entering the kidneys to the urinary bladder contents. A conceptual difference between the proposed model and the model in Figure 4 is that the proposed model treats the

kidneys much differently from other exchangeable tissues, primarily by depicting a far higher rate of exchange between kidneys and plasma than assigned to other tissues. Also, in contrast to the model in Figure 4, the proposed model depicts slow return of nickel to plasma from a portion of the "Body sink".

The structure of the proposed model is shown in Figure 7. Transfer coefficients are listed in Table 2. The model divides systemic nickel into the following compartments: Plasma, RBC, a rapid-turnover kidney compartment (Kidneys 1), a slow-turnover kidney compartment (Kidneys 2), a liver compartment with a moderate turnover rate (Liver 1), a liver compartment with slow turnover (Liver 2), four bone compartments (cortical and trabecular surface and volume), a compartment of other soft tissues with a moderate turnover rate (ST0), and a compartment of other soft tissues with a slow turnover rate (ST1). Removal of systemic nickel from the body is depicted as occurring along three pathways: in urine after a brief residence in the kidneys and urinary bladder content, in feces after secretion into the alimentary tract, and all other excretion pathways combined (e.g., sweat, saliva, hair, and nails).

The proposed model depicts renal clearance of plasma nickel as the net result of the following events. Nickel circulating in plasma is filtered at the glomerulus and briefly retained in a kidney compartment named Kidneys 1. Part of the nickel deposited in Kidneys 1 is removed to the urinary bladder contents and the remainder is reabsorbed to blood. Based on findings for 26 electrolytic refinery workers (Nieboer et al., 1992) it is assumed that 30% of nickel entering Kidneys 1 moves to Urinary bladder content and 70% returns to Plasma. To achieve renal clearance of 3.8 d^{-1} (Figure 3) the transfer coefficient from Plasma to Kidneys 1 is set at 3.8 d^{-1} /

0.3 = 12.7 d^{-1}. The total outflow rate from Kidneys 1 is set at 50 d^{-1}, which yields a reasonable fit to data on uptake and retention of ^{63}Ni in rats following intravenous administration of $^{63}NiCl_2$ (Smith and Hackley, 1968). Based on the total outflow rate of 50 d^{-1} from Kidneys 1, the transfer coefficient from Kidneys 1 to Plasma is 0.7 x 50 d^{-1} = 35 d^{-1}, and the transfer coefficient from Kidneys 1 to Urinary bladder content is 0.3 x 50 d^{-1} = 15 d^{-1}. A small portion (~0.0025%) of nickel leaving Kidneys 1 is assigned to the long-term retention kidney compartment (Kidneys 2), but the content of Kidneys 2 makes virtually no contribution to the predicted nickel content of kidneys during the early days after acute input to blood.

It is assumed that urinary excretion accounts for 85% of cumulative biological removal of systemic nickel and the remaining 15% is equally divided between feces and other combined excretion pathways (Other excreta in Figure 7). Fecal excretion is assumed to result from secretion of nickel into the alimentary tract contents, transfer of unabsorbed nickel into the colon contents, and subsequent removal from the colon contents in feces. It is assumed that half of the amount excreted in feces arises from biliary secretion (transfer from Liver 1 to SI content) and half arises from other secretions into the contents of the alimentary tract, depicted for simplicity as transfer from Plasma to SI content. Transfer coefficients describing movement of nickel from Plasma and Liver 1 into SI content and from Plasma into Other excreta are derived from these assumptions. For example, after the transfer coefficient from Plasma to Liver 1 is set, the fraction of outflow from Liver 1 to SI content is set so that endogenous fecal excretion due to biliary secretion represents 7.5% / 2 = 3.75% of total excretion, after reabsorption from SI content is taken into account (f_A is assumed to be 0.05 for purposes of these derivations).

Transfer coefficients describing exchange of nickel between Plasma and RBC are set for consistency with observations for a human subject following ingestion of a stable nickel tracer (Patriarca et al., 1997).

Animal studies have yielded variable results concerning fractional uptake of nickel by liver and bone but generally indicate that the content of each of these organs is considerably less than that of the kidneys during the early hours or days. A reasonable representation of the comparative nickel contents of kidneys, liver, and bone in the early hours after administration of ^{63}Ni to laboratory animals is achieved by assuming that the liver receives 5% of the total transfer of 9 d^{-1} from Plasma to compartments with a moderate turnover rate (Liver 1, Trabecular surface, Cortical surface, and Other 0), and the roughly threefold more massive bone receives 15%. These percentages correspond to deposition of ~1.9% in liver and ~5.7% in bone surface when expressed in terms of total outflow from plasma. Nickel depositing in bone is assumed to be divided equally between Trabecular surface and Cortical surface. The transfer coefficients implied by these assumptions are as follows: Plasma to Liver 1, $0.05 \times 9\ d^{-1} = 0.45\ d^{-1}$; Plasma to Trabecular surface or Plasma to Cortical surface = $(0.15 \times 9\ d^{-1}) / 2 = 0.675\ d^{-1}$.

It is assumed that 40% of activity deposited in Liver 1 transfers to the SI contents, 8% transfers to the long-term retention compartment Liver 2, and the rest returns to plasma. The transfer coefficients from Liver 1 to SI contents and Liver 1 to Liver 2 are calculated from this division of outflow together with the assigned transfer rate of 1.9 d^{-1} from Liver 1 to Plasma. The fractional transfer from Liver 1 to SI content is set so that biliary secretion represents 50% of total endogenous fecal excretion of nickel as discussed earlier. The fractional transfer from

Liver 1 to Liver 2 is set to yield a reference steady-state concentration of nickel in liver as described later.

For lack of more definitive information on nickel retention in bone it is assumed in the proposed model that 99% of nickel depositing in the bone surface compartments transfers to Plasma at 1.9 d^{-1} (the transfer coefficient from Plasma to Body sink + Feces in Figure 4) and the other 1% transfers to the corresponding bone volume compartment (implying a transfer coefficient of 0.0192 d^{-1}). Nickel depositing in the bone volume compartments is assumed to be transferred to plasma at the reference rates of bone turnover.

The transfer coefficient 7.2 d^{-1} from Plasma to Other 0 is calculated as 9 d^{-1} minus the sum of transfer coefficients to Liver 1, Cortical surface, and Trabecular surface. The compartment Other 1 represents long-term retention of nickel in soft tissues other than liver and kidneys. The transfer coefficient from Plasma to Other 1 is set at 1.2 d^{-1}, the rounded difference between 1.9 d^{-1} and the sum of net transfers from Plasma to excretion pathways other than renal excretion and net transfers to slow-turnover compartments of the liver, kidneys, and bone. Although the derivation of transfers to the slow-turnover compartments of the liver, kidneys, and bone depend in turn on the transfer rate to Other 1 (as indicated below), the low transfers assigned to those compartments are within the rounding error for transfer to Other 1.

Excluding long-term retention in bone volume, which is addressed above, parameter values describing long-term retention and excretion of nickel are selected to reproduce reference (typical) concentrations of stable nickel in tissues and urine of adult members of the general

population as determined from a review of the literature. It is taken into account that many of the reported concentrations, particularly older values, are likely to overestimate typical values for the general population due to inadequate analytical sensitivity, difficulty in avoiding nickel contamination, and matrix interferences. The following values are selected as reference concentrations: urine, 2 μg L^{-1} (see the review of Templeton et al., 1994a, and the original data and review of Ohashi et al., 2006); all soft tissues, 0.01 μg g^{-1} (see the original data and review of Rezuke et al., 1987). These reference values imply a total-body content of about 0.7 mg of nickel in the reference adult male, compared with the value of 10 mg given in ICRP Publication 23 (1975) and used to develop the nickel model currently used by the ICRP.

It is assumed that the removal half-time to Plasma is the same for all soft-tissue compartments with slow turnover. This half-time is derived from the reference nickel concentration in soft tissues (0.01 μg g^{-1}) and the assumption of continuous input to blood of the reference adult male at the rate 4 μg Ni d^{-1}. The input rate 4 μg Ni d^{-1} is a rounded value based on the reference concentration of nickel in urine (2 μg L^{-1}), a daily urine volume of 1.6 L (ICRP, 2002), and assumption that urinary excretion of nickel represents 85% of total excretion of systemic nickel at steady-state. This approach seems preferable to basing nickel input to blood on a typical value for dietary nickel together with a typical value for absorption of ingested nickel, both of which involve sizable variability and uncertainty. A rounded removal half-time from slow-turnover soft tissue compartments of 400 d produces a steady-state nickel concentration of ~0.01 μg g^{-1} in Other soft tissues. The fractional transfers from Kidneys 1 to Kidneys 2 and from Liver 1 to Liver 2 are based on this derived removal half-time and a reference nickel concentration of 0.01 μg g^{-1} in these tissues.

Model predictions of plasma clearance of nickel and cumulative urinary excretion of nickel are virtually identical to the modified Sunderman model curves shown in Figures 5 and 6 respectively (which are based on the underlying modified Sunderman model shown in Figure 4). Model predictions of uptake and retention of nickel by the kidneys are compared in Figure 8 with data for rats (Smith and Hackley, 1968). Predictions of uptake and retention by RBC are compared in Figure 9 with observations for a human subject who ingested the stable nickel tracer ^{62}Ni (Patriarca et al., 1997). As discussed above, the model is designed to reproduce typical concentrations of nickel in urine and soft tissues of the general population as estimated from modern data. The derivation of parameter values for bone does not depend on an estimate of the typical concentration of bone in the general population because a typical concentration of nickel in bone cannot be determined from the variable reported data. A reference concentration of nickel is not required in the development of parameter values for plasma or RBC, which are based entirely on short-term studies on human subjects. However, the steady-state concentration of nickel in plasma predicted by the model (0.3 μg L^{-1}) is reasonably consistent with the results of modern studies of the concentration of nickel in plasma and serum (Sunderman et al., 1989; Templeton et al., 1994a). A typical steady-state concentration of nickel in RBC cannot be determined with much confidence from available information.

DISCUSSION AND CONCLUSIONS

The biokinetic model for nickel currently recommended by the ICRP (Figure 1) was adopted in the late 1970s and modified in the early 1990s to include explicit excretion pathways. The model

was designed as a mathematically convenient tool for estimating committed doses from radio-nickel intake and does not depict realistic paths of movement of nickel in the body.

The ICRP currently is updating its biokinetic and dosimetric models for occupational intakes of radionuclides. The updated biokinetic models continue a trend in recent ICRP reports toward physiological realism. In addition to predicting the cumulative activity of radionuclides in major repositories in the body, the updated models are intended for bioassay interpretation and extension to special problems such as transfer of radionuclides from the mother to the fetus or nursing infant. The model structures generally include one or more compartments representing blood, depict recycling of activity between tissues and blood, and, where feasible, reflect physiological processes that influence rates of transfer of internally deposited radionuclides.

Compared with the ICRP's current model, the model for systemic nickel described in this paper is based on a larger set of observations of the behavior of nickel in human subjects and laboratory animals and provides a more realistic description of the paths of movement of nickel in the body. The proposed model predicts substantially lower cumulative activities of important radioisotopes of nickel in systemic pools and hence substantially lower radiation doses to tissues than does the current ICRP model.

Table 3 compares predictions of cumulative activity (total nuclear transformations over 50 y following intake) in selected systemic regions based on the proposed model (PM) and the current ICRP model systemic nickel in adults (ICRP, 1993, 1994), for direct input (intravenous injection) of ^{63}Ni into blood. Column 2 lists the cumulative activities of ^{63}Ni in specified regions

of the body. The comparisons with the ICRP Publication 67, 1993 ("Pub67") model are shown in Columns 3 and are expressed as ratios A:B, where A is the derived cumulative activity in a given tissue based on the proposed model and B is the corresponding value based on the ICRP Pub67 model. All regions addressed explicitly in the ICRP Pub67 model are also addressed explicitly in the proposed model, but some regions addressed explicitly in the proposed model are contained implicitly in "Other tissue" in the ICRP Pub67 model. In such a case the cumulative activity in the region based on the ICRP Pub67 model is taken as the mass of the region as a fraction of the mass of Other tissue (based on reference tissues masses given in ICRP Publication 23, 1975, which were used in the ICRP Pub67 dosimetry system), times the cumulative activity in "Other" (Figure 1) predicted by the ICRP Pub67 model. The sizable differences in some of the regional cumulative activities predicted by the two models result from some combination of differences in model formulations, the data sets addressed in model development, and the method of development of parameter values.

Table 4 compares dose coefficients for ^{63}Ni based on the proposed model and the ICRP Pub67 model assuming direct input of ^{63}Ni to blood. The dosimetry system of ICRP Publication 67 was used to compute both sets of dose coefficients. This includes the tissue weighting factors used to calculate the effective dose, i.e., these weighting factors were taken from ICRP Publication 60 (1991). As indicated in Table 4, the proposed model yields considerably lower dose coefficients for all tissues than does the ICRP Pub67 model.

Comparisons of the proposed model and the ICRP Pub67 model similar to those shown in Table 3 and Table 4 were also done for ^{59}Ni, the other important radioisotope of nickel. The resulting ratios, PM : ICRP Pub67, for ^{59}Ni were virtually identical to those determined for ^{63}Ni.

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LIST OF FIGURE CAPTIONS

Figure 1. Current biokinetic model of the International Commission on Radiological Protection (ICRP) for systemic (absorbed) radio-nickel in workers or adult members of the public (ICRP, 1993, 1994).

Figure 2. Structure of the biokinetic model of Onkelinx et al. (1973) for systemic nickel based on data for rats and rabbits injected with $^{63}NiCl_2$. Compartment V2 exchanges nickel with the central compartment V1 over a period of hours or days. Body sink represents slowly exchangeable or non-exchangeable nickel including nickel entering excretion pathways other than urine and faeces (e.g., hair).

Figure 3. Biokinetic model for systemic nickel developed by Sunderman et al. (1989) from measurements of the nickel concentration in serum and excreta of 10 subjects following acute ingestion of elevated masses of stable nickel in water.

Figure 4. A modified version of the model of Sunderman et al. (1989) that provides better agreement with results of the nickel tracer study of Patriarca et al. (1997).

Figure 5. Comparison of predictions of plasma clearance of nickel based on modified Sunderman model (Figure 4) with original model (Sunderman et al., 1989; also see Figure 3) and with representative data of Patriarca et al. (1997).

Figure 6. Comparison of predictions of cumulative urinary excretion of absorbed nickel based on modified Sunderman model (Figure 4) with original model (Sunderman et al., 1989; also see Figure 3) and with mean values (darkened circles) and ranges (vertical lines) determined by Patriarca et al. (1997).

Figure 7. Structure of the proposed model for systemic nickel. UB = urinary bladder, RBC = red blood cells, SI = small intestine.